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Chronic brain damage in sickle cell disease and its relation with quality of life☆

Elena Cela[a,*], Ana G. Vélez[b], Alejandra Aguado[c], Gabriela Medín[d], José M. Bellón[d], Cristina Beléndez[a]

[a] Hematología Pediátrica, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain
[b] Estudiante de pregrado de Medicina, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain
[c] Servicio de Radiodiagnóstico Pediátrico, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain
[d] Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

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ABSTRACT

Background and objective: Sickle cell anemia causes progressive organ damage. The objective is to describe school performance of patients with sickle cell anemia and their clinical parameters and quality of life that may have an influence. The hypothesis is that if school alterations occur without other objective data, additional factors must be present besides the disease itself.
Patients and methods: Transversal study performed in November 2015 considering analytical variables, complications and neuroradiological images of children with sickle cell anemia, and family survey on school performance and quality of life.
Results: Median age was 6.8 years and 78% were diagnosed at birth. Sixty patients were included. School performance was altered in 51% of cases and was related to nocturnal hypoxemia. Acute stroke incidence was 6.7%. Transcranial ultrasound was abnormal in 4% of cases and magnetic resonance imaging in 16% of cases. Quality of life showed pathological findings in all areas and the low values increased proportionally in older ages. The stroke affected the physical and social sphere, and lung disease affected the physical and emotional spheres.
Conclusions: Poor school performance affects half of the patients and it is related to nocturnal hypoxemia, although other socio-cultural factors may have an influence. Quality of life is affected in most of these cases independently of academic results. The absence of alterations in neuroimaging or the apparent lack of severe clinical parameters do not mean that quality of life and schooling are normal.

Lesión crónica cerebral en la anemia falciforme y su relación con la calidad de vida

Palabras clave:
Anemia de células falciformes
Calidad de vida
Trastornos neurocognitivos
Neuroimagen

RESUMEN

Antecedentes y objetivo: La anemia falciforme provoca una lesión orgánica progresiva. El objetivo de este trabajo es describir el rendimiento escolar de pacientes con anemia falciforme y los parámetros clínicos y de calidad de vida que pueden influir. La hipótesis es que si las alteraciones escolares se presentan sin otros datos objetivos, factores añadidos deben concurrir aparte de la propia enfermedad.
Pacientes y métodos: Estudio transversal realizado en noviembre de 2015 considerando variables analíticas, complicaciones e imágenes neurorradiológicas de niños con anemia falciforme, y encuesta familiar sobre rendimiento escolar y calidad de vida.

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* Corresponding author.
E-mail address: elena.cela@salud.madrid.org (E. Cela).

Resultados: Se incluyeron 60 pacientes. La mediana de edad fue de 6,8 años, y el 78% se diagnosticaron al nacimiento. El rendimiento escolar estaba alterado en el 51% y se relacionó con hipoxemia nocturna. El accidente cerebrovascular se presentó en el 6,7%. La ecografía doppler transcraneal fue patológica en el 4% y la resonancia magnética en el 16%. La calidad de vida arrojó resultados patológicos en todas las esferas y aumentó la proporción con valores bajos a mayor edad. El accidente cerebrovascular afectó la esfera física-social, y la neumopatía, la física-emocional.
Conclusiones: El fracaso escolar como expresión de lesión crónica cerebral en la anemia falciforme afecta a la mitad de los pacientes y se relaciona con hipoxemia nocturna, aunque otros factores de confusión socioculturales pueden influir. La calidad de vida está alterada en la mayoría de los niños, independientemente del retraso escolar. La ausencia de una lesión orgánica objetiva en la neuroimagen o de parámetros de gravedad clínica no implican que la calidad de vida o la escolarización sean normales.

Introduction

Sickle cell anemia (SCA) is an inherited disease characterized by chronic haemolytic anemia and vascular occlusions, which cause acute pain by ischemia, and a chronic progressive organ damage. The most devastating complication is *acute cerebrovascular accident* (ACVA) by large vessel involvement. Primary prevention of the same is done by assessing its risk according to cerebral blood flow measured by transcranial Doppler ultrasound (TCDUS). There is also a brain microvasculature disorder, which, in the majority of cases, does not present symptoms (they are called silent infarctions), but appears to be associated with impaired cognitive function.[1–3] Overall, cerebrovascular disease produces the lowest IQs if there is ACVA, intermediate values if silent infarctions are present, and figures around 90 even in children without abnormalities in neuroimaging.

SCA is characterized by the presence of hemoglobin S (HbS), resulting from the substitution of valine by glutamic acid at amino acid position 6 of β globin chain. The presence of HbS causes an Hb tetramer (alpha2/betaS2) which is insoluble when deoxygenated, causing the deformation of the erythrocyte until it acquires a sickle shape, decreasing the elasticity of the same. The disease may be revealed through the presence of homozygous HbS (SS) or its heterozygous combination with another mutation of the β globin chain (HbS-beta thalassemia, HbSC).[4–6] HbS gene is distributed worldwide, most often in sub-Saharan Africa and Central and South America. This high prevalence in certain regions of the world seems to reflect the protective effect of the mutation against *Plasmodium falciparum*. It is the most common hemoglobinopathy in the United States, with an incidence of one case per 625 live births. In Spain, the prevalence has increased in the last 2 decades by increased immigration, and in some communities, there has been an incidence of one case per 5000 newborns.[7]

In the neonatal screening, it can be diagnosed by chromatography through the heel prick test or when the clinical signs and symptoms appear, at later ages.[8] The universal new-born screening was introduced in the Community of Madrid in 2003, in the Basque Country in 2011, Valencia in 2012, and the rest of the Spanish regions progressively from 2015.

Treatment is based on health education for recognizing warning symptoms, vaccination against encapsulated bacteria, penicillin prophylaxis, transfusions in selected situations, stimulating production of fetal hemoglobin and, in selected cases, hematopoietic stem cell transplantation from matched sibling.[9]

Silent infarcts are a major manifestation of cerebral vascular disease in these patients, which alter neurocognitive function.[1] They are detected in magnetic resonance imaging (MRI) using the sequences T1, T2 and FLAIR, and it includes lesions related to leukoencephalopathy, infarction and encephalomalacia.[10] They are the result of occlusion of small vessels, and usually appear in the arterial border zones. Therefore, the terminology used is misleading, because although it alludes to its imaging diagnosis

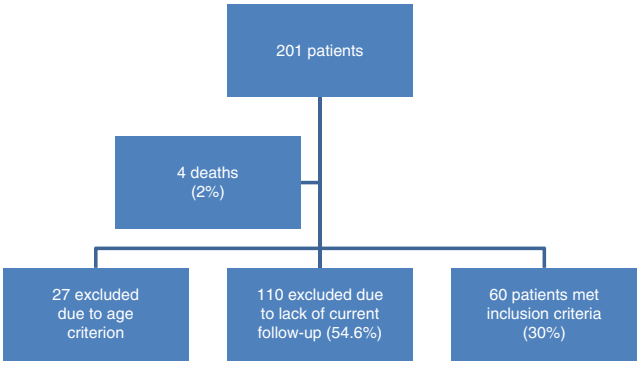

Fig. 1. Patient selection.

without obvious neurological symptoms, the neurocognitive test abnormalities can be remarkable, and the association with a subsequent frank stroke seems clear.[11] Neurocognitive impairment and poor school performance may be multifactorial, including objective brain injuries and other psychosocial factors,[12] as deterioration has also been detected in young children in whom illness severity was not yet a determining factor.[13] In the United States, the socioeconomic status and a troublesome family environment is associated with low academic level.

The aim of this paper is to describe student performance in our healthcare environment of a group of children with SCA that may be associated with chronic brain injury, reflected in clinical and laboratory parameters, alterations in neuroimaging or socio-cultural problems, and also evaluating the quality of life. The hypothesis is that if changes in school and quality of life occur early, before they are detected in the objective imaging or clinical tests, other factors must be present, apart from the disease itself.

Patients and method

Cross-sectional study in November 2015 at a single university hospital. Patients included were a cohort of children with SCA under follow-up since their diagnosis in the Pediatric Haemoglobinopathies Unit that met the following criteria at the study's cut-off point: age between 2 and 18 years, have gone at least once to medical consultation in the last year, to be alive, informed consent from parents and accepting to answer a survey. The study was approved by the Ethics Committee of the center.

Out of a total of 201 patients diagnosed with SCA, 60 children met the inclusion criteria (Fig. 1). Exclusions were due to death, not meeting the age criteria or because the family could not be traced (54%). Of these, 15% had returned to their home countries and the rest did not respond to calls. There were no differences between the latter and those selected in terms of sex, age, time of diagnosis or genotype. A review of electronic medical records was